PATENT

#25
B. Webb
8/2/00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
OLUFUNMILAYO I. OLOPADE

Serial No.: 08/674,311

Filed: July 1, 1996

For: METHYLTHIOADENOSINE PHOSPHORYLASE COMPOSITIONS AND METHODS OF USE IN THE DIAGNOSIS AND TREATMENT OF PROLIFERATIVE DISORDERS

Group Art Unit: 1655

Examiner: LISA ARTHUR

Atty. Dkt. No.: ARSB:509—1/MBW

CERTIFICATE OF MAILING
37 C.F.R 1.8

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7/6/2000
Date

Mark B. Wilson

I. RESPONSE TO OFFICE ACTION DATED FEBRUARY 8, 2000 AND
II. REQUEST FOR EXTENSION OF TIME

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants respectfully submit a Response to the Official Action mailed February 8, 2000 (the "Action"). A response to the Action is due on July 8, 2000, by virtue of the enclosed Petition for Extension of Time and payment of the appropriate fees.

Reconsideration of the application is respectfully requested.

PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicant petitions for an extension of time of two months, to and including July 8, 2000, in which to respond to the Office Action dated February 8, 2000. Pursuant to 37 C.F.R. § 1.17, a check in the amount of $190.00 is enclosed, which is the process fee for a two-month extension of time. If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Assistant commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/ARSB:509--1/WIM.

RESPONSE TO OFFICE ACTION

A. State of the Claims

At the time of the Action, claims 39-96 were pending. No claims have been added or deleted. Therefore, claims 39-96 are currently pending. For the convenience of the Examiner, a copy of the pending claims is attached hereto as Exhibit A.

B. The 35 U.S.C. § 102(b) Rejections Over Kamb et al. are Overcome.

Claims 39-50, 52-57, 59, 60, 67-76, 78, 80-83, 88-94 are rejected under 35 U.S.C. § 102(b) as anticipated by Kamb et al. Kamb et al. is said to teach isolated polynucleotides containing the tumor suppressor gene MTS1 which maps to 9p21-22 and is tightly linked to MTAP. The cosmid of Kamb et al. is said to comprise the sequence of SEQ ID NO. 1 and, therefore, reasons that the polynucleotide of Kamb et al. comprises at least 21, 30, 40 or all contiguous bases from nucleotides 122-970 of SEQ ID NO 1. The Action states that the

polynucleotide sequence of Kamb et al. inherently meets the limitations of claims 45 and 46. Kamb et al. is further said to teach a method for detecting a nucleic acid comprising a sequence encoding MTAP by hybridization by a probe comprising at least 21 bases of SEQ ID NO 1.

Applicant respectfully traverses these rejections.

Kamb et al. appears to describe work aimed at searching for candidate tumor suppressor genes. During this search, parts of cosmid C5 were sequenced and identified as the MTS1 and MTS2 genes. The 9p21 region contains multiple genes in addition to MTS1 and MTS2. The publication reports DNA sequences for the two closely related genes MTS1 and MTS2 but does not identify, isolate or sequence a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1 of the present invention. The entire cosmid C5 was not sequenced. Even if the cosmid C5 comprised MTAP, Kamb et al. did not disclose a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1, or a polynucleotide comprising a sequence region that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2.

As is well established by the courts, conception of a gene requires isolation of the gene, or defining the gene so as to distinguish it from other materials, as well as how to make it. *Amgen, Inc. v. Chugai Pharmaceutical Company, Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991) ("When an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred (i.e., until after the gene has been isolated").

Kamb et al. do not disclose a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Prior to the disclosure of SEQ ID NO:1 by Applicant, there was no understanding of where the sequence encoding a methylthioadenosine phosphorylase polypeptide

was located. As a consequence, the anticipation rejections are overcome. Applicant respectfully requests the withdrawal of these rejections.

C. The 35 U.S.C. § 102(b) Rejections Over Bohlander et al. are Overcome.

Claims 39-48, 50-60, 67-76, 78-83 and 88-94 are rejected under 35 U.S.C. § 102(b) over Bohlander et al., which is said to teach chromosome fragments, vectors and host cells comprising the MTAP gene and methods of use identical to the claimed invention. The Action reasons that chromosome fragments that comprise the MTAP gene inherently comprise SEQ ID NO 1 encoding a polypeptide of SEQ ID NO 2.

Bohlander et al. describe several DNA probes, based on DNA fragments from a microdissected chromosomal fragment taken from 15 chromosomes in the region 9p21-23. At most, the paper reveals that some of the single copy clones originating from the 9p21-23 area of the chromosome are useful probes from this region of the chromosome. Applicant respectfully suggests that Bohlander, *et al.* merely describe probes that may ultimately lead to the identification, isolation and characterization of novel tumor suppressor genes in the 9p21 region. Bohlander et al. refers only to the existence of the MTAP gene; it in no way discloses a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Indeed, Bohlander et al. expressly states at page 215 that the position of the MTAP gene is not known at the time of publication ("The relative position on the map of the *Not*I site and the *MTAP* gene is uncertain at the present time."). Bohlander et al. further state on page 215 that "two line of evidence suggest that there might be tumor suppressor genes other than *MTS1* and *MTS2* located in the region centromeric to the *INF* gene cluster" (emphasis added). The possible presence of another tumor suppressor gene in this region does not teach the location of a polynucleotide comprising a

nucleic acid sequence from SEQ ID NO:1. Bohlander et al. had not isolated or identified a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Merely stating the existence of the MTAP gene is insufficient to anticipate a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. *See, Amgen, Inc. v. Chugai Pharmaceutical Company, Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991). Bohlander et al. does not provide a sequence encoding the MTAP gene, and cannot anticipate the present invention.

Applicant respectfully requests withdrawal of these rejections.

D. The 35 U.S.C. § 102(b) Rejections Over Scaletti et al. are Overcome.

Claims 95 and 96 are rejected under 35 U.S.C. § 102(b) as anticipated by Scaletti et al., which is said to disclose methods of distinguishing tumor types by comparing chromosome 9p patterns between tumor types.

Applicant has studied the abstract by Scaletti et al. and fails to find a description of distinguishing tumor types by comparing chromosome 9p patterns. The cell lines studied indicate normal chromosome 9 findings on all but two cell lines. Those two cell lines show a deletion and in one an additional inversion. In fact, the abstract notes that, while the enzyme MTAP is deficient in acute leukemia cases, it is apparently "not associated with a frequent cytogenetic abnormality of chromosome 9p". It appears to applicant, therefore, that Scaletti et al. were not able to distinguish tumor types by comparing chromosome 9p patterns. This publication in no way anticipates the use of a nucleic acid sequence from SEQ ID NO:1 pattern of 9p homozygous deletions and associating the patterns with patterns obtained from the tumor to be identified.

The anticipation rejections are overcome. Applicant respectfully requests the withdrawal of these rejections.

E. The 35 U.S.C. § 102(b) Rejections Over Nobori et al. are Overcome.

Claims 39-42, 45-66, 74-75, 77-83 and 88-94 are said to be anticipated by or, in the alternative, obvious over Nobori et al. (1994), which is said to teach that methylthioadenosine phosphorylase cDNA was isolated and a 2-kilobase fragment was found to contain the 3' end of the MTAP gene. Nobori et al. (1994) is said to have used this sequence as a probe for chromosome walking. The Action argues that, although Nobori et al. (1994) only disclose a 3' fragment of the human MTAP gene, the claims as written read on polynucleotides containing fragments of the MTAP gene as small as 10 bases.

The Nobori et al. (1994) publication reports the sequence analysis of the CDK4I coding region of a lymphoblastoid cell line and speculates that the CDK4 inhibitor is a strong candidate for a melanoma susceptibility gene. A 19-kb λ-phage clone designated 10B1 was subcloned and a fragment of CDK4 inhibitor gene identified. The subclone was said to contain an open base reading frame with a sequence identical to the 3' region of a previously reported CDK4 inhibitor. The Norobi et al. (1994) reference showed a physical map of chromosome 9p21 between two gene loci (i.e., MTAP and IFN-β). However, the physical map shown is incorrect, as confirmed by Nobori et al. in *Proc. Natl. Acad.. Sci. USA* 3:6203-6208 (1996). The Nobori et al. (1996) reference discloses at page 6207 that the correct gene order on human chromosome 9p is p15—p16—MTAP—IFNα from centromeric to telomeric (p15 and p16 code for a 15-kDa protein and a 16-kDa protein, respectively, that inhibit CDK4). Therefore, the deleted region in T98G is the

region containing p16, centromeric to MTAP, but not the previously proposed region between MTAP and IFNA gene loci. *Id.*

Thus, the Nobori et al. (1994) references discloses the wrong map of cDNA. This reference would lead those of ordinary skill in the art to look in the wrong place for a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1.

Furthermore, Nobori et al. (1994) had only a small fragment of the MTAP gene, and did not disclose the sequence of even that small fragment. Characterization, isolation and sequencing of a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1 were not disclosed by Nobori et al. (1994) and probes from the 3' end of the MTAP gene were, in fact, employed to study absence or rearrangement of the CDK4 inhibitor gene in malignant cell lines, not to isolate, sequence and characterize a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1.

Applicant again directs the Examiner's attention to *Amgen, Inc. v. Chugai Pharmaceutical Company, Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991), which confirms that conception of a gene requires isolation of the gene, or defining the gene so as to distinguish it from other materials, as well as how to make it. Applicant concludes that Nobori et al. do not disclose a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1 because the nucleic acid sequence from SEQ ID NO:1 had not been isolated and sequenced, nor is there mention of kits or methods of use for a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. The anticipation rejections over Nobori et al. (1994) are overcome. Applicant respectfully requests the withdrawal of these rejections.

F. The 35 U.S.C. § 103(a) Rejections are Overcome.

Claims 39-42, 45-66, 74-75, 77-83 and 88-94 are said to be obvious over Nobori et al. (1994). Nobori is said to teach that methylthioadenosine phosphorylase cDNA was isolated and a 2-kilobase fragment was found to contain the 3' end of the MTAP gene. Nobori et al. (1994) is said to have used this sequence as a probe for chromosome walking. The Action argues that, although Nobori et al. (1994) only disclose a 3' fragment of the human MTAP gene, the claims as written read on polynucleotides containing fragments of the MTAP gene as small as 10 bases. The Action asserts that claims limited to a polynucleotide consisting of the MTAP gene would have been *prima facie* obvious over Nobori et al. (1994) because Nobori et al. (1994) discloses a highly specific probe for isolating the complete coding sequence for the MTAP gene. According to the Action, the ordinary artisan would be highly motivated to obtain the remainder of the MTAP gene.

Applicant respectfully traverses these rejections.

As stated above regarding the 35 U.S.C. § 102(b) rejection, the Nobori et al. (1994) publication reports that a 19-kb λ-phage clone designated 10B1 was subcloned and a fragment of CDK4 inhibitor gene identified. The subclone was said to contain an open base reading frame with a sequence identical to the 3' region of a previously reported CDK4 inhibitor. The Norobi et al. (1994) reference showed a physical map of chromosome 9p21 between two gene loci (i.e., MTAP and IFN-β). However, the physical map shown is incorrect, as confirmed by Nobori et al. in *Proc. Natl. Acad.. Sci. USA* 3:6203-6208 (1996). The Nobori et al. (1996) reference discloses at page 6207 that the correct gene order on human chromosome 9p is p15—p16—MTAP—IFNA from centromeric to telomeric (p15 and p16 code for a 15-kDa protein and a 16-kDa protein,

respectively, that inhibit CDK4). Therefore, the deleted region in T98G is the region containing p16, centromeric to MTAP, but not the previously proposed region between MTAP and IFNA gene loci. *Id.*

Thus, the Nobori et al. (1994) references discloses the wrong map of cDNA. This reference would lead those of ordinary skill in the art to look in the wrong place for a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Norbori et al. (1994) consequently teaches away from the present invention, rendering the present invention nonobvious. Proceeding contrary to the accepted wisdom of the prior art is strong evidence of nonobviousness. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983); *In re Hedges,* 783 F.2d 1038 (Fed. Cir. 1986). An invention's contradicting the teachings and express expectations of the prior art has long been a criterion of patentability. *Racal-Vadic, Inc. v. Universal Data Systems,* 207 U.S.P.Q. 902 (Ala. 1980).

The Action asserts that Nobori et al. (1994) disclose a highly specific probe for isolating the complete coding sequence for the MTAP gene, and that the ordinary artisan would be highly motivated to obtain the remainder of the MTAP gene. However, at best, in view of Nobori et al. (1994), one skilled in the art might find it obvious to try to obtain the remainder of polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. This is not the standard of 35 U.S.C. § 103. *In re Geiger,* 815 F.2d 686 (Fed. Cir. 1987). "'Obvious to try' has long been held not to constitute obviousness." *In re Deuel,* 51 F.3d 1552 (Fed. Cir. 1995) (citing *In re O'Farrell,* 853 F.2d 894 (Fed. Cir. 1988)). An "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result or indicate that the claimed result would be obtained if certain directions

were pursued. *In re Eli Lilly & Co.*, 902 F.2d 943 (Fed. Cir. 1990). A particular result, such as the sequence of a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1, is not made obvious by a general incentive, nor by the existence of techniques by which those efforts can be carried out. *In re Deuel,* 51 F.3d at 1559. "The fact that one can conceive a general process in advance for preparing an undefined compound does not mean that a claimed specific compound was precisely envisioned and therefore obvious." *Id.* Given that the map disclosed by Nobori et al. (1994) was incorrect and that the reference did not disclose the sequence of any part of a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1, let alone isolate and characterize a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1, Nobori et al. (1994) does not contain sufficient teaching to render the present invention *prima facie* obvious.

Claims 84-87 are rejected as being obvious over Nobori et al. (1994) or Bohlander et al., both of which are said to teach the association of the 9p21-22 region with cancers due to its frequent deletion in patients with various cancers and teach that this region was suspected to contain a number of tumor suppressor genes. The Action argues that it would have been *prima facie* obvious to one of ordinary skill in the art to have packaged the polynucleotides and vectors taught by Nobori et al. (1994) or Bohlander et al. with detection reagents in a kit in order the achieve the expected benefit of providing probes to use in a method of screening for deletions of the 9p21-22 region as suggested by Nobori et al. (1994) and Bohlander et al. in a convenient form.

Applicant respectfully traverses this rejection.

Claims 84-87 of the present invention claim a detection kit comprising a first nucleic acid segment comprising at least 21 contiguous nucleotides of SEQ ID NO:1. Neither Nobori et al.

(1994) nor Bohlander et al. disclose any contiguous nucleotide of SEQ ID NO:1. Nobori et al. (1994) discloses merely a 3' fragment of the human MTAP gene, and none of the sequence of the gene. Further, Nobori et al. (1994) discloses the wrong map of cDNA, and would lead those of ordinary skill in the art to look in the wrong place for a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Norbori et al. (1994) consequently teaches away from the present invention, rendering the present invention nonobvious. As stated above, proceeding contrary to the accepted wisdom of the prior art is strong evidence of nonobviousness. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983); *In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986). An invention's contradicting the teachings and express expectations of the prior art has long been a criterion of patentability. *Racal-Vadic, Inc. v. Universal Data Systems*, 207 U.S.P.Q. 902 (Ala. 1980).

Bohlander et al. describe probes that may ultimately lead to the identification, isolation and characterization of novel tumor suppressor genes in the 9p21 region. Bohlander et al. refers only to the existence of the MTAP gene; it in no way discloses any part of the a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. Although the Action claims that the chromosome fragments of Bohlander et al. that comprise the MTAP gene inherently comprise SEQ ID NO:1, inherency may not be established by probabilities or possibilities. *Hansgirg v. Kemmer*, 102 F.2d 212 (C.C.P.A. 1939); *In re Oelrich et al.*, 666 F.2d 578 (C.C.P.A. 1981). Bohlander et al. expressly state at page 215 that the position of the MTAP gene is not known at the time of publication. Bohlander et al. further state on page 215 that "two lines of evidence suggest that there might be tumor suppressor genes other than *MTS1* and *MTS2* located in the region centromeric to the *INF* gene cluster" (emphasis added). Case law establishes that the disclosure of the possible presence of another tumor suppressor gene in this region does is

insufficient to establish inherency. "The fact that a certain thing may result from a given set of circumstances is not sufficient." *Hansgirg v. Kemmer,* 102 F.2d at 214; *In re Oelrich et al.,* 666 F.2d at 581.

For the reasons above, Applicant respectfully requests withdrawal of the § 103(a) rejections.

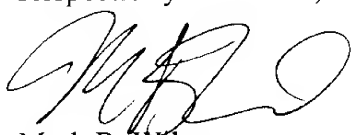
G. Conclusion

Applicant submits that none of the references cited by the action anticipates or renders obvious the subject matter disclosed and claimed in the present application. Applicant is the first to have isolated and sequenced a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. The enzyme encoded by the gene had been previously known; however, only the general location of the MTAP gene was recognized. As noted by the court in *Amgen, Inc.,* "...conception has not been achieved until reduction to practice has occurred, *i.e.* until after the gene has been isolated." *Amgen, Inc. v. Chugai Pharmaceutical Company, Ltd.,* 927 Fed. 2d at 1206. None of the references had identified the structure or physical characteristics of the MTAP gene.

The action's position appears to be that because a large piece of DNA that may contain the MTAP gene but which has not been sequenced and from which the MTAP gene has not been isolated, anticipates or renders obvious a polynucleotide comprising a nucleic acid sequence from SEQ ID NO:1. This contradicts the position taken by the courts which have repeatedly emphasized that a gene is a chemical compound and that conception of chemical compounds require the definition of that compound (see *Okaa*, 849 F2d at 583, 7 U.S.P.Q. 2d at 1171, 1988).

Applicant intends this to be a complete response to the examiner's action and reconsideration of the application is respectfully requested. Should any further issues remain, the undersigned attorney respectfully requests a telephone call at (512) 418-3035.

Respectfully submitted,



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